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Why are they having infant colic? A nested case–control study

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Summary

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We aimed to analyse infant (birth characteristics, feeding type, faecal enzyme activities) and environmental (maternal smoking, nutrition and psychological status, mother–child bonding, family structure, support for the mother, familial atopy) risk factors for infant colic and to follow infants with respect to physical growth, sleeping status up to 8 months of age in a nested case–control study. 660 mothers who delivered at Dr Zekai Tahir Burak Maternity Hospital, were enrolled within 3–72 h post delivery. Each infant with inconsolable persistent crying and four matched infants with no crying episodes were invited by phone to Hacettepe University Ihsan Doğramacı Children's Hospital at 30–45 days post partum. At 40–55 days, we examined the infants and gave mothers a questionnaire, including crying characteristics of the infants; 47 infants were diagnosed with colic and 142 as non-colic. When the infants were 7–8 months old, another interview was done. The colic group had higher proportions of less-educated (≤8 years) and smoking mothers, extended family and families with domestic violence than the non-colic group. The colic group of mothers had significantly higher rates of 'impaired bonding' in the Postpartum Bonding Questionnaire, higher scores on the Edinburgh Postnatal Depression Scale, higher scores for hostility subscales of the Brief Symptom Inventory and a more irregular sleep pattern than the non-colic group. No differences were revealed for faecal enzyme activities. At 7–8 months, the colic group was shorter than the non-colic group. Colic was associated with various perinatal factors (maternal education, smoking habits, cheese consumption, hostility scores and domestic violence) and having colic in infancy negatively affected the sleeping pattern and the height of the infant.

Keywords: *infant colic*, *infant feeding*, *faecal enzyme activities*, *maternal depression*, *post-partum bonding*, *infant growth*, *infant sleep*, *maternal smoking*, *maternal diet*.

Introduction

Colic, one of the most common problems during infancy, consists of a behavioural syndrome characterised by paroxysmal, excessive, inconsolable crying without identifiable cause in an otherwise healthy infant.[1–3] Its pathogenesis remains unclear.[1] Infant colic (IC) has been attributed to several factors including the infants' difficult temperament,[4] inadequate or inappropriate mother–infant interaction, mothers' anxiety,[5–7] abnormal gastrointestinal function,[8,9] allergic problems such as exposure to cows' milk proteins in formula or breast milk,[10,11] and prenatal or postnatal exposure to tobacco smoking.[12–15] The interactions between these factors might mask or influence risks.

We investigated those maternal, family and infant factors that possibly have a role in the development of colic, such as sociodemographic characteristics, family structure, maternal psychopathology, domestic violence, post-partum mother–child bonding, maternal smoking exposure, maternal nutrition during

pregnancy and after delivery, familial atopy, infant's diet and certain faecal bacterial enzyme activities (urease, beta-glucosidase, beta-glucuronidase) in a nested case–control study. In addition, we interviewed infants at 8 months of age to detect whether IC could change the feeding and sleeping behaviour of infants.

Materials and methods

Study setting and subjects

Infants born in Dr Zekai Tahir Burak Maternity Hospital in Ankara, Turkey between July–September 2006 were invited to participate in a nested case–control study according to crying episodes of infants within 1.5–2 months of age.

Study timing

V1: All mothers within the first 3 days after delivery [Visit 1] were interviewed (Figure 1). Enrolled volunteer mothers were requested to respond to a questionnaire that included sociodemographic characteristics, medical and obstetric history (type of delivery, birthweight, gestational age), active–passive maternal smoking during pregnancy and domestic violence. Maternal haemoglobin values, analysed on the first day postpartum, were noted from the hospital records. Then, all the mothers were assessed by the Brief Symptom Inventory (BSI) as a measure of the mother's psychological status.[16] The BSI consists of 53-item self-reported symptoms drawn from the Symptom Checklist-90-R and assesses current psychological symptomatology.[17,18] It results in three global indices (global severity index, positive symptom distress index, positive symptom total index) and subscales (somatisation, obsessive-compulsiveness, depression, anxiety, paranoid ideation, psychoticism).

P1: When infants were 1–1.5 months of age, mothers were interviewed by phone (P1). If the mother reported any infant crying lasting for ≥2 h per day, occurring in ≥3 days per week and recurring for at least 3 weeks, the infants were accepted as 'possibly colic' and invited to Hacettepe University Ihsan Doğramacı Children's Hospital. After each possible colic case, the next four infants who had no colic crying were invited to be examined at the same hospital.

V2: All the examinations were performed by one study paediatrician when the infants were 1.5–2 months of age. During this visit, infants were examined for the presence of any organic conditions that may have led to excessive crying such as otitis media, fractures, urinary infections or chronic illness including inherited metabolic disorders, immune deficiency disorders or whether they had received either antibiotics or probiotics in the week preceding recruitment. The infants with organic pathologies were not included in the study. The remaining 'possible colic cases' comprised the IC group. Infants who had no crying episodes during the phone interview (P1) were included in the non-colic (NC) group. However, those infants who had no history of crying during P1 and showed pathologic crying at V2, were also evaluated for 'possible colic' and included in the IC group.

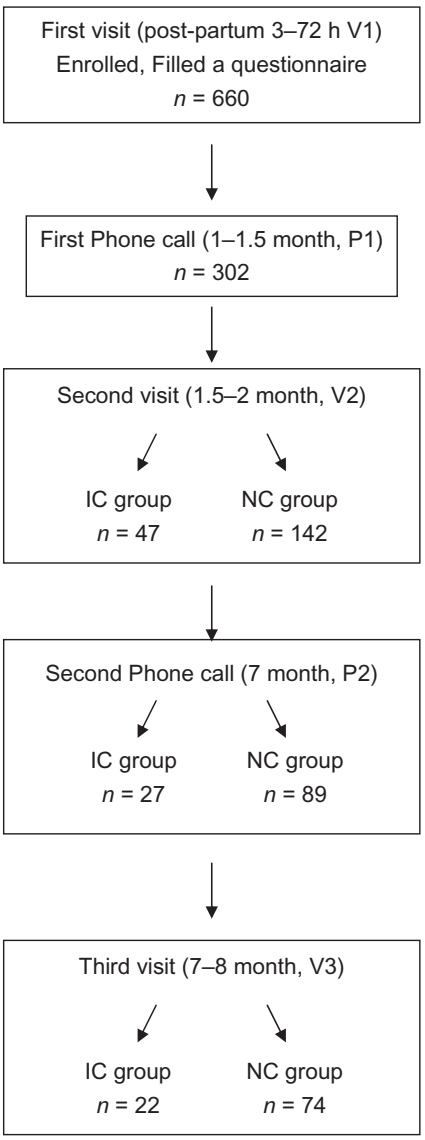

Figure 1. Follow-up scheme of the study.

All enrolled infants aged 1.5–2 months were assessed by a questionnaire, which included crying characteristics (occurrence time in the day, length of the crying episodes and the infant's behaviour), type of feeding, bottle-pacifier use, stool consistency and frequency. Any symptoms of atopic disease during the study period were recorded. Infants were weighed and height measured. To aid the uniform documentation of crying times, one of the researchers was always available to help the parents by telephone. Stool samples were obtained from the infants to analyse activities of the faecal enzymes.

Additionally, maternal smoking and dietary habits, and family history of atopy were determined at V2. Atopy was considered positive if the infant had ≥1 family member (mother, father and/or older sibling) with atopic eczema, allergic rhinitis or asthma. The maternal dietary assessment was based on a semi-quantitative food frequency questionnaire, consisting of commonly used foods in the Turkish cuisine possibly related to colic such as milk, yoghurt, cheese, egg, grains, bulgur, dried legumes (including dried bean, chickpea, pea, lentil, broad bean) cayenne pepper, nuts, onion, broccoli, cauliflower, cabbage, chocolate, tomatoes and fish in the last week and a 24-h dietary recall. Also, we recorded any differences in diet from the pregnancy period.

Mothers were administered three psychological scales. The Postpartum Bonding Questionnaire (PBQ) has 25 items with 6-point Likert scales; it is used to assess mother–infant bonding and consists of four subscales: impaired bonding, rejection and anger, anxiety about care, risk of abuse.[19] The Mother-to-Infant Bonding Scale (MIBS) is an 8-item questionnaire with 4-point Likert scales; it detects how the mother is feeling about her child. A high score indicates worse mother-to-infant bonding.[20] The Edinburgh Postnatal Depression Scale (EPDS) is a validated, self-rating 10-item questionnaire developed to identify post-partum depression.[21,22]

P2: Telephone interviews were repeated when the infants reached 7 months and the participants were invited for a physical examination.

V3: They were also re-evaluated by a second questionnaire, which included a second EPDS for mothers, crying characteristics of the infant, type of feeding, bottle-pacifier use, maternal smoking habits and family history of atopy at 7–8 months of age. Anthropometric measurements and the Denver II Test for infants were carried out. The Denver II test is based on observation and caretakers' reporting of the child's skills in personal–social, fine motor, language and gross motor areas using a standard test form and kit. Denver II results were interpreted as: two or more delayed items scored as 'abnormal', one delay and one caution, as 'questionable', and no delays or one caution, as 'normal'.[23]

Methods of faecal enzyme activity

The faecal samples were collected in plastic cups and stored at −20°C until analysis and pH measurements were done in supernatant using pH paper. Then, faecal samples were thawed and carefully mixed with a spatula and suspended (1:10 w/v) in cold 0.1 mmol/L phosphate buffer (pH 7.0). The faecal pellets were sonicated for 30 s and centrifuged at 2000 *g* for 5 min to separate out the non-bacterial debris. The supernatant fraction was decanted and stored in ice in stoppered plastic tubes and used immediately for assay of total proteins and enzymatic activities.[24] Faecal protein determinations were done in duplicate based on the method of Lowry *et al*.[25] using bovine serum albumin as the standard. Faecal beta-glucuronidase and beta-glucosidase activity was determined according to Perrin-Guyomard *et al*.[26] and faecal urease activity according to the method of Ling *et al*.[24] with slight modifications.

Statistical analyses

Data were analysed using SPSS-Windows (SPSS Inc, Chicago, IL, USA). The normality of data distribution was checked using the Kolmogorov–Smirnov test. Because the distributions of faecal urease, β-glucosidase, β-glucuronidase activity and MIBS were skewed, the Mann–Whitney *U*-test was used for comparison. Independent sample *t*-tests were applied to the continuous variables with normal distributions. For comparing proportions χ^2 or Fisher's exact test was used when applicable.

Average weekly consumption of food items was calculated from the food frequency questionnaire. Maternal anaemia was defined as a Hb value less than 11 g/dl. *Z* scores of weight for age, weight for height, height for age and body mass index for age (WAZ, WHZ, HAZ and BAZ) were calculated from the WHO Multicentre Growth Reference Study.[27] Anthropometric measurements taken at 7–8 months of age were compared after adjusting for birthweight, gestational age and gender.

To identify the perinatal predictors of IC we offered to backward logistic regression the factors including maternal age, maternal education level (≤8 years vs. >8 years), extended family structure vs. simple, maternal occupation vs. housewife, planned pregnancy (yes vs. no), domestic violence vs. no violence, any maternal psychological problems during pregnancy needing a physician's help (yes vs. no), family history of atopy (yes vs. no), smoking exposure during pregnancy (yes vs. no), maternal Hb <11 g/dl vs. ≥11 g/dl, type of delivery (caesarean section vs. vaginal), birth order (1 vs. >1), gender (female vs. male), birthweight <2500 g vs. ≥2500 g, gestational age <37 weeks vs. ≥37 weeks, hostility scores of brief symptom inventory, maternal cheese consumption during pregnancy, maternal hospitalisation during pregnancy (yes vs. no), history of having had another infant with colic (yes vs. no), given breast milk as the first food (yes vs. no), breast fed within the first 2 h (yes vs. no). Data are presented as mean ± SD or median (25–75th percentile) or *n* (%). Statistical significance level was set at $P < 0.05$.

Ethics

This study was approved by the Ethical Committee of The Faculty of Medicine, Hacettepe University. Infants were enrolled in the study after written informed consent was obtained from the parents.

Results

At V1, 660 mothers agreed to participate during the enrolment period (Figure 1) and answered the first questionnaire. After 1–1.5 months, only 302 (45.8%) mothers were reached by phone. There were no significant differences between mothers enrolled and mothers who completed a telephone interview with respect to maternal age, education, employment status, BSI scores, infant gender, birthweight, gestational age, birth order, maternal smoking, type of delivery and family type.

At P1, the overall prevalence of colic was 16.6% (50/302). These 50 infants and following 200 infants without pathological crying were invited to our clinic for further evaluation. In all, 189 mother–infant pairs participated in V2. All infants were assessed once again for colic diagnosis; 47 otherwise healthy infants had had colic crying (IC group) whereas the remaining 142 infants were in the NC group. When the infants reached 7–8 months of age, 27 IC cases and 89 NCl cases were reached by phone (P2) and 22 IC cases and 74 controls attended the hospital for V3.

Crying characteristics

Daily average (±SD) crying time of the IC group was 151 (±37) min. The mean (±SD) age at commencement of attacks of screaming was 21.6 (±13.0) days. Weekly mean (±SD) crying frequency was 7.5 (±3.5). Crying episodes occurred in the evening in 31 cases (66.0%). Mothers of the IC group stated that the episodes of colic were associated with maternal diet in 32 (68.1%) and hunger crying in 6 (12.8%) cases. Crying was unpredictable and spontaneous. Colic episodes were accompanied with flushed face, furrowed brow, clenched fists and pulling legs up to the stomach in 41 infants (87.2%) and with breath holding in 14 infants (29.8%). To manage colic episodes, parents had used several methods, such as hugging the baby (36.1%), rocking (12.8%), moving the legs (6.4 %), riding around (6.4%), massaging the stomach (6.4%) and feeding (2.1%). Five infants (10.6%) were preterm and 3 (6.4%) had low birthweight. The mean (±SD) age at resolution of the crying episodes was 4.0 (±1.4, min–max = 1.5–6) months.

In the NC group at V2, 40 of 102 mothers complained about their babies' crying, but none of these cases complied with the diagnostic criteria of IC. Attacks of screaming had begun at 20.6 ± 17.2 days. The mean crying duration for these infants was 12.4 ± 13.7 min/day.

Comparisons between IC and NC groups

Infant gender, gestational age, birth order, mode of delivery and birthweight were similar between the IC and NC groups (Table 1). Only 2.1 % of infants had taken no breast milk at V2. There were no differences in the first food taken after delivery, breast-feeding characteristics (sucking period in a session and frequency of breast feeding), starting age of pacifier use, daily duration of pacifier use, vitamin use or any history of bottle use (for water or formula) between birth and V2 (Table 1). However, pacifier use in the IC group was higher than the NC group but the difference was not statistically significant (57.4%, 43.0%, respectively; $P = 0.06$).

Mean diaper usage was similar in the two groups; however, the mean number of diaper changes with

Table 1. Characteristics of infant colic (IC) and non-colic (NC) groups

		IC Group	NC Group	OR [CI]/Mean difference [CI]
V1 (on admission)	*n*	47	142	
	Male sex	20 (42.6)	67 (47.2)	0.83 [0.43, 1.61]
	Birth order, first	28 (59.6)	69 (48.6)	1.56 [0.80, 3.04]
	Gestational age <37 weeks	5 (10.6)	14 (9.9)	1.09 [0.37, 3.20]
	Birthweight, <2500 g	3 (6.4)	9 (6.3)	1.01 [0.26, 3.89]
	Birthweight, *z* scores	–0.17 ± 0.91	–0.06 ± 1.02	–0.11 [–0.44, 0.23]
	Delivery type, CS	24 (51.1)	70 (49.3)	1.07 [0.56, 2.08]
	Given breast milk as the first food after delivery	43 (91.5)	131 (92.3)	0.90 [0.27, 2.98]
	Breast fed within the first 2 h	32 (68.1)	99 (69.7)	0.93 [0.46, 1.89]
V2 (1.5–2 months)	Being breast fed	46 (97.9)	139 (97.9)	0.99 [0.10, 9.78]
	Sucking period in a breast-feeding session, min	13 (10–20)	15 (10–30)	
	Breast-feeding frequency at night	5.1 ± 3.2	4.9 ± 2.8	0.21 [–0.75, 1.17]
	Breast-feeding frequency in daytime	7.5 ± 2.7	7.5 ± 2.9	0.03 [–0.90, 0.96]
	Vitamin usage	25 (54.3)	77 (54.2)	1.01 [0.52, 1.96]
	Infants who had taken any formula from birth to V2	14 (29.8)	44 (31.0)	0.95 [0.46, 1.94]
	Infants with any bottle-feeding from birth to V2	10 (21.3)	43 (30.3)	0.62 [0.28, 1.36]
	First age for bottle-feeding, days	11 (1–30)	15 (3–25)	
	Pacifier use	27 (57.4)	61 (43.0)	1.79 [0.92, 3.49]
	Starting age for pacifier use, days	9 (7–20)	10 (3–25)	
	Duration of daily pacifier use (min/day)	30 (10–60)	20 (10–30)	
	Overall daily diaper changed	5.8 ± 1.9	5.5 ± 2.0	0.23 [–0.43, 0.89]
	Daily change of diaper with stool**	4.4 ± 2.4	3.3 ± 2.1	1.09 [0.37, 1.80]
	Sleeping pattern: regular*	23 (48.9)	94 (66.2)	0.49 [0.25, 0.96]
	Sleeping place			
	Same room, same bed	5 (10.6)	8 (5.6)	1.00 Reference
	Same room, separate bed	37 (78.7)	120 (84.5)	0.49 [0.15, 1.60]
	Separate room	5 (10.6)	14 (9.9)	0.57 [0.13, 2.60]
	Sleep duration in daytime, hours**	4.8 ± 2.1	6.0 ± 2.4	–1.15 [–1.97, –0.33]
	Sleep duration at night, hours**	5.7 ± 2.2	6.8 ± 2.1	–1.14 [–1.88, –0.39]
	Weight for age, *Z* scores	–0.63 ± 1.02	–0.60 ± 1.20	–0.03 [–0.42, 0.37]
	Height for age, *Z* scores	–0.82 ± 1.20	–0.76 ± 1.38	–0.05 [–0.52, 0.41]
	Weight for height, *Z* scores	0.20 ± 0.99	0.20 ± 1.38	0.01 [–0.44, 0.45]
	Body mass index for age, *Z* scores	–0.29 ± 0.92	–0.27 ± 1.26	–0.02 [–0.43, 0.38]
P2 (7 months)	*n*	27	89	
	Being breast fed	22 (81.5)	70 (78.7)	1.19 [0.40, 3.57]
	Age of complementary feeding, months	5.6 ± 1.3	5.6 ± 1.1	–0.01 [–0.51, 0.49]
	Sleeping duration in daytime, hour (07:00–21:00)	3.4 ± 1.3	3.6 ± 1.7	–0.16 [–0.79, 0.47]
	Sleeping duration at night, hour (21:00–07:00)	8.8 ± 2.1	8.5 ± 1.7	–0.34 [–1.15, 0.47]
V3 (7–8 months)[a]	*n*	22	74	
	Weight for age, *Z* scores	0.02 ± 1.04	0.36 ± 1.05	–0.34 [–0.84, 0.17]
	Height for age, *Z* scores**	–0.25 ± 1.21	0.43 ± 1.01	–0.68 [–1.19, –0.18]
	Weight for height, *Z* scores	0.33 ± 1.05	0.28 ± 1.11	0.05 [–0.48, 0.58]
	Body mass index for age, *Z* scores	0.24 ± 1.07	0.16 ± 1.11	0.07 [–0.46, 0.60]

Values were presented as mean ± standard deviation and mean difference [95% confidence interval]; *n* (%) and odds ratio [95% confidence interval]; median (25–75th percentile).

*$P < 0.05$, **$P < 0.01$.

[a]Adjusted for birthweight, gestational age, gender.

stools was higher in the IC group than the NC group at V2 (4.4 vs. 3.3/day, $P = 0.003$).

Based on maternal report, regular sleeping pattern was seen more frequently in the NC group than the IC group (66.2% vs. 48.9%, $P = 0.035$, Table 1). Sleep duration, both in daytime and at night, was shorter in the IC group than that in the NC groups at V2 (4.8 vs. 6.0 h in daytime, $P = 0.006$; 5.7 vs. 6.8 h at night, $P = 0.003$). However, the sleeping place was similar in both groups.

Table 2. Characteristics of mothers and families in colic (IC) and non-colic (NC) groups

Characteristics	IC	NC	OR [CI]/Mean difference [CI]
n	47	142	
Maternal age, years	24.7 ± 4.7	25.3 ± 5.3	−0.54 [−2.25, 1.18]
Maternal education level ≤8 years**	40 (85.1)	92 (64.8)	3.11 [1.30, 7.44]
Employed mothers	3 (6.4)	13 (9.2)	0.68 [0.18, 2.49]
Family income monthly <250$	8 (17.0)	25 (17.7)	0.95 [0.40, 2.28]
Extended family structure*	26 (55.3)	55 (38.7)	1.96 [1.01, 3.82]
Planned pregnancy	31 (66.0)	104 (73.2)	0.71 [0.35, 1.44]
Help to become pregnant	2 (4.3)	8 (5.6)	0.74 [0.15, 3.64]
Maternal health problem during pregnancy	8 (17.0)	41 (28.9)	0.51 [0.22, 1.17]
Maternal hospitalisation during pregnancy	4 (8.5)	8 (5.6)	1.56 [0.45, 5.43]
Maternal anaemia at the first day post partum, Hb < 11 g/dl	17 (36.2)	57 (40.1)	0.85 [0.43, 1.67]
Parental harmony	44 (93.6)	132 (93.0)	1.11 [0.29, 4.22]
Domestic violence**	7 (14.9)	4 (2.8)	6.04 [1.68, 21.67]
Maternal psychological problems, last year	1 (2.1)	4 (2.8)	0.75 [0.08, 6.88]
Any maternal psychological problem with physician help	6 (12.8)	17 (12.0)	1.08 [0.40, 2.91]
History of maternal depression, lifelong	2 (4.3)	4 (2.8)	1.53 [0.27, 8.65]
History of having another infant with colic	15 (32.6)	38 (27.1)	1.20 [0.63, 2.67]
Family history of atopy	11 (23.4)	42 (29.6)	0.73 [0.34, 1.56]
Smoking exposure during pregnancy**			
Maternal smoking	15 (31.9)	20 (14.1)	4.02 [1.67, 9.68]
Environmental smoking exposure	18 (38.3)	47 (33.1)	2.05 [0.93, 4.51]
No smoking exposure	14 (29.8)	75 (52.8)	1.00 Reference
Post-partum smoking exposure at V2			
Maternal smoking	11 (23.4)	22 (15.5)	2.12 [0.83, 5.43]
Environmental smoking exposure	23 (48.9)	65 (45.8)	1.50 [0.69, 3.23]
No smoking exposure	13 (27.7)	55 (38.7)	1.00 Reference
Support for infant care by husband	29 (59.6)	86 (60.6)	0.96 [0.49, 1.88]
Support area of husband			
Housework	14 (29.8)	47 (33.3)	0.85 [0.41, 1.74]
Infant feeding	4 (8.5)	22 (15.5)	0.51 [0.17, 1.56]
Sleeping infant**	23 (48.9)	44 (31.0)	2.13 [1.09, 4.19]
Giving a bath to infant	12 (25.5)	37 (26.1)	0.97 [0.46, 2.07]
Making infant wear	9 (19.1)	23 (16.2)	1.23 [0.52, 2.88]
Changing infant diaper	6 (12.8)	15 (10.6)	1.24 [0.45, 3.40]
Having an assistant (other than husband) for infant care	29 (61.7)	74 (52.1)	1.48 [0.76, 2.91]
Presence of boarding guest during post-partum period	24 (51.1)	91 (64.1)	0.59 [0.30, 1.14]

Values were presented as Mean ± standard deviation and mean difference [95% confidence interval]; *n* (%) and odds ratio [95% confidence interval].
*$P < 0.05$, **$P < 0.01$.

When assessed at V3, age at start of complementary foods, duration of exclusive breast feeding and the duration of day and night sleep were similar in both groups (Table 1).

Family characteristics

The proportion of mothers educated for less than 8 years was significantly higher in the IC group than the NC group (85.1% vs. 64.8%, $P = 0.009$). Monthly family income, the proportion of mothers employed, planned pregnancies and parental harmony were similar in both groups (Table 2). However, the presence of domestic violence was higher in the IC group than the NC group (14.8% vs. 2.8%, $P = 0.002$). Extended family structure in the IC group was higher than the control group (55.3% vs. 38.7%, $P = 0.046$). There were no significant differences in percentages of anaemic mothers, having ever had another infant with colic or atopic disease in the family (Table 2).

At V2, mothers having someone to assist with infant care, including the husband and the presence of

boarding guests at home during the post-partum period were similar in both groups (Table 2). When areas of support (feeding, sleeping, making infant clothes, changing diaper and housework) were analysed, it was clear that assistance to mothers with infant sleeping was significantly more in the IC group than those in the NC group (64.5% vs. 37.6%, $P = 0.007$).

Cigarette exposure

Maternal smoking during pregnancy was reported significantly more often in the IC than the NC group (cases with active, passive and no smoking exposure were 31.9%, 38.3% and 29.8% for IC group and 14.2 %, 32.6% and 53.2%, for NC group, respectively, $P = 0.006$). Also, the median (25–75th percentile) number of smoked cigarettes (both active and environmental exposure) during pregnancy was 5/day (0–20) in the IC group and 0/day (0–4) in the NC group ($P < 0.001$). However, the frequencies of post-partum smoking exposure were not different between the groups (Table 2).

Maternal nutrition

At V2, mothers were asked about the average weekly consumption of foods probably related to colic. From the foods considered, including milk, yoghurt, cheese, egg, grains, cayenne pepper, nuts, onion, broccoli, cauliflower, cabbage, chocolate and tomato, mothers of the NC group consumed significantly more cheese before and after pregnancy and tomatoes after pregnancy than mothers of the IC group.

The average cheese consumption during pregnancy was 184 g/week in the IC group and 223 g/week in NC group (difference between means [95% CI] = –40 [–76, –4], $P = 0.030$) and the average cheese consumption during the lactation period was 184 in the IC group and 234 g/week in the NC group (difference between means [9 % CI] = –50 [–94, –6], $P = 0.027$). During the lactation period, the IC and NC groups consumed 225 g/week, and 334 g/week of tomatoes respectively (difference between means [95% CI] = –109 [–206, –13], $P = 0.027$).

Changing growth parameters over time

The mean *Z* scores of birthweights were similar in the two groups (Table 1). The mean weight for height, weight for age and body mass index for age were similar when the infants were 1.5–2 months and 7–8 months. Despite the similarity of height for age at V2, at V3, the mean height for age was significantly lower in the IC compared with the NC group (–0.25 vs. 0.43, $P = 0.009$). After adjusting for gender, gestational age and *z* scores of birthweight, height for age at 7–8 months remained lower in the IC group than that in the NC group ($P = 0.003$).

Assessment of infants' development

Of the IC group, 21 (91.3%) had a normal Denver II test result at V3. One case was questionable and one case was abnormal. The results of 68 cases in NC group (89.5%) were normal, seven cases were questionable and one case was abnormal.

Psychopathologies of mother and mother–infant bonding assessment

Among the maternal BSI scores including the three indexes (global severity index, positive symptom total index, positive symptom distress index) and nine subscales (somatisation, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism), only the mean score for hostility subscale was higher in IC than NC cases (0.77 vs. 0.53, $P = 0.011$, Table 3).

The IC group had more cases with impaired bonding in the PBQ than the NC group at V2 (21.3%, 9.9%, respectively, $P = 0.042$). However, the percentages of mothers with 'rejection and anger', 'anxiety about care' and 'risk of abuse' were similar in both groups. Also the mean MIBS scores were not different in the groups.

The mean EDPS score of IC group at V2 was significantly higher than the NC group (10.6 ± 5.6, 7.0 ± 4.6, respectively, $P < 0.001$). The percentage of cases with pathological EPDS at V2 was higher in IC group than NC group (36.2%, 10.6%, respectively, $P < 0.001$). Interestingly, cases with pathological EPDS at V2 had higher post-partum hostility scores than others (0.83 ± 0.51, 0.54 ± 0.55, respectively, $P = 0.009$). However, there was no difference in the percentage of mothers with pathological EPDS between groups at V3 (19.0%, 20.5%, respectively, $P > 0.05$). Similarly, cases with pathological EPDS at V3 had higher post-partum hostility scores than others (0.89 ± 0.69, 0.50 ± 0.53, respectively, $P = 0.010$).

Faeces characteristics

Thirty-four IC and 66 NC infants gave stool samples at V2. However, 16 stool samples (10 IC, 6 NC) did not

Table 3. Brief Symptom Inventory (BSI), Postpartum Bonding Questionnaire (PBQ), Mother-to-Infant Bonding Scale (MIBS), Edinburgh Postnatal Depression Scale (EPDS) scores

			IC Group	NC Group	OR [CI]/Mean difference [CI]
V1 (on admission)	*n*		47	142	
	BSI	Global severity index	0.67 ± 0.48	0.62 ± 0.55	0.05 [–0.13, 0.23]
		Positive symptom total index	20.0 ± 10.4	18.6 ± 11.8	1.36 [–2.52, 5.24]
		Positive symptom distress index	1.67 ± 0.55	1.63 ± 0.53	0.04 [–0.14, 0.22]
		Somatisation	0.83 ± 0.70	0.79 ± 0.65	0.04 [–0.18, 0.26]
		Obsession-compulsion	0.69 ± 0.63	0.61 ± 0.64	0.08 [–0.13, 0.29]
		Interpersonal sensitivity	0.86 ± 0.71	0.72 ± 0.69	0.14 [–0.09, 0.37]
		Depression	0.71 ± 0.60	0.65 ± 0.74	0.05 [–0.19, 0.29]
		Anxiety	0.77 ± 0.66	0.70 ± 0.73	0.07 [–0.17, 0.31]
		Hostility*	0.77 ± 0.57	0.53 ± 0.54	0.23 [0.05, 0.42]
		Phobic fear	0.37 ± 0.51	0.42 ± 0.56	–0.05 [–0.24, 0.13]
		Paranoid ideation	0.59 ± 0.72	0.58 ± 0.76	0.02 [–0.23, 0.26]
		Psychoticism	0.27 ± 0.38	0.34 ± 0.52	–0.07 [–0.23, 0.10]
V2 (1.5–2 months)	*n*		47	142	
	PBQ	Impaired bonding*	10 (21.3)	14 (9.9)	2.47 [1.02, 6.02]
		Rejection and anger	0 (0.0)	1 (0.7)	–
		Anxiety about care	3 (6.4)	3 (2.1)	3.16 [0.62, 16.22]
		Risk of abuse	2 (4.3)	2 (1.4)	3.11 [0.43, 22.73]
	MIBS score		2.61 ± 2.73	2.11 ± 2.48	0.50 [–0.34, 1.35]
	EPDS score	≥13**	17 (36.2)	15 (10.6)	4.80 [2.16, 10.68]
V3 (7–8 months)	*n*		21	73	
	EPDS score	≥13	4(19.0)	15 (20.5)	0.91 [0.27, 3.11]

Values are presented as mean ± standard deviation and mean difference [95% confidence interval]; *n* (%) and odds ratio [95% confidence interval].

*$P < 0.05$, **$P < 0.01$.

BSI, Brief Symptom Inventory; PBQ, Postpartum Bonding Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; MIBS, Mother-to-Infant Bonding Scale; IC, Infant Colic; NC, non-colic.

contain sufficient particles and could not be analysed. The median values of stool pH, urease, beta-glucuronidase and beta-glucosidase enzyme activities were similar in both groups (Table 4).

Multivariable logistic regression analysis (backward LR) showed that maternal education ≤8 years (OR = 3.22 [95% CI 1.24, 8.36], $P = 0.016$), presence of domestic violence (OR = 8.96 [95% CI 1.85, 43.42], $P = 0.006$), smoke exposure during pregnancy (OR = 1.98 [95% CI 0.92, 4.24], $P = 0.080$), hostility scores (OR = 2.02 [95% CI 1.04, 3.91], $P = 0.038$) and prenatal cheese consumption (OR = 0.89, [95% CI 0.79, 0.99], $P = 0.030$) were independent perinatal predictors of IC cases (Table 5).

Table 4. Faecal enzyme activities and pH in infant colic (IC) and non-colic (NC) groups at post-partum 1.5–2 month (V2)

	IC Group	NC Group
n	24	60
pH	7 (7–7.75)	7 (7–7)
Urease, μmol/mg/min	1.2 (1.1–1.8)	0.9 (0.7–1.4)
β-glucosidase, μmol/mg-protein/min	5.6 (4.1–7.8)	6.1 (3.8–8.1)
β-glucuronidase, μmol/mg-protein/min	11.1 (8.8–12.8)	12.5 (7.0–21.4)

Values were presented as median (25–75th percentiles).

Discussion

In the present study, the overall prevalence of IC was found to be 16.6% at 1.5–2 months of age at the first phone interview. In the literature the prevalence of IC has varied from 8% to 40% according to the definition.[2,28–33] In the present study, no statistical significance was detected between IC and NC infants according to gender, gestational age, birthweight, type of delivery, infant's feeding pattern, birth order or maternal age. However, lower maternal education and the extended family were found to be more prevalent

Table 5. Perinatal factors affecting infant colic according to multivariable logistic regression (backward logistic regression) analysis

	OR [CI]
Maternal education level, ≤8 years vs. >8 years*	3.22 [1.24, 8.36]
Domestic violence vs. no violence*	8.96 [1.85, 43.42]
Smoking exposure during pregnancy, yes vs. no	1.98 [0.92, 4.24]
Hostility scores of Brief Symptom Inventory*	2.02 [1.04, 3.91]
Maternal cheese consumption during gestational period*	0.89 [0.79, 0.99]

*$P < 0.05$.

among the IC group. Similarly, most of the previous studies reported no difference according to gender in occurrence of colic.[28–30,32] Talachian *et al*.[33] reported first-born infants and boys to have a higher rate of colic. Contrary to the present study, Crowcroft *et al*.[30] reported advanced age and primigravidae as at higher risk of IC, but Lucassen *et al*.[2] reported no such differences. The influence of socio-economic class on IC is also controversial.[2,11,31,32,34] It is apparent from previous investigations that even when a large population is studied, it is impossible to identify a single most important risk factor for IC, as the interactions between socio-economic, psychosocial and psychological factors are very complex. This is probably one of the explanations for the lack of agreement in the literature.

Infantile colic might be initiated by an unstable psychosocial environment of the infant (behavioural hypothesis).[5–7] Previously, maternal stress, anxiety and depression have been defined as risk factors affecting the baby's well-being starting from pregnancy.[5,6,35] In contrast with Rautava *et al*.[34] we did not observe a greater chance of occurrence among children whose parents reported poor adaptation to pregnancy, or diseases during pregnancy. However, infants from families with domestic violence had a higher risk for IC in both univariable and multivariable analyses in the present study. On the other hand, maternal psychopathology (apart from hostility) was similar in both groups during the early post-partum period (assessed prior to colic episodes). In addition, IC itself might cause maternal stress. Interestingly, when EPDS was applied at post-partum 1.5–2 months, mothers living with infants with colic had post-partum depression more frequently than mothers of infants without colic episodes in both univariable and multivariable analyses. Similarly, Vik *et al*.[7] also reported that infant crying was associated with high EPDS scores (OR: 4.4 [95% CI 2.4, 8.2]) at the second post-partum month in a cross-sectional study. Also, Akman *et al*.[5] reported that depression scores were higher and maternal insecure attachment style was greater in infants with colic than infants without colic. When the PBQ assessed mother–infant bonding, the IC group had a significantly higher frequency of impaired bonding than the control group at post-partum 1.5–2 month (V2). However, MIBS scores were similar. Conflicting results in different tests might be due to differences in the sensitivity of tests. The parents of infants with colic may feel tired and inadequate, and be worried that their child has a serious medical disorder. In families with such infants, there may be problems in communication and family functioning, as well as parental anxiety and fatigue.[36] When superimposed on poor communication skills within the family, colic may damage family dynamics. Given the high percentages of IC in families with domestic violence and mothers with impaired bonding, physicians must watch for signs of family distress and assess the family's coping resources. Infants with colic had a slightly higher risk of abuse than the control group but this was not statistically significant in the present study. Also, Lee *et al*.[37] reported that infants with colic were more frequently exposed to physical violence including the shaken baby syndrome. Therefore, while evaluating IC, clinicians should consider the risk of child abuse and check psychological environment of infants with colic at child health supervision visits. After resolution of IC, mothers of the IC group had similar EPDS scores to mothers of the control group. Thus, living with a colicky infant might result in deterioration of the psychological status of mothers. On the other hand, Clifford *et al*.[12] reported some lasting effect of IC on levels of maternal anxiety or depression after colic resolved. Also, Vik *et al*.[7] found that mothers of infants with colic had increased odds of having high EPDS scores 6 months after delivery even if the crying had resolved (OR: 3.7 [95% CI: 1.4, 10.1]).

Maternal smoking during pregnancy was associated with IC; however, post-partum smoking had no significant effect in the present study. In a community-based trial, Canivet *et al*.[38] found that daily maternal smoking in pregnancy was related to subsequent colic; however, the association between smoking at infant age 5 weeks and colic had not reached statistical sig-

nificance. Some studies reported an increased risk for IC in both smoking during pregnancy and the postpartum period.[13,15] In other studies an influence of paternal smoking was also detected.[29,32] Moreover, it was suggested that smoking is linked to increased plasma and intestinal motilin levels[39] and higher-than-average intestinal motilin and ghrelin levels seem to be related to an elevated risk of IC.[14]

Infant feeding characteristics (exclusive or predominant breast feeding) had no relationship with IC in the present study. Previous studies reported controversial results.[11,29–31,34] However, since most of the infants in the present study were breast fed, a larger number of non-breast fed cases might have affected the significance level. Because the incidence of colic in breast fed and bottle-fed infants is similar, mothers who are breast feeding should be encouraged to continue.

It has been speculated that colic may be a result of abdominal cramping and hyperperistalsis. Gut hormones such as motilin are thought to cause hyperperistalsis, leading to abdominal pain and colic.[8,9,14] Interestingly, daily stool frequency was higher in the IC than the NC group in the present study. Given the hypothesis of gastrointestinal pathology in IC, stool urease, beta-glucosidase and beta-glucuronidase enzyme activities were analysed; however, the levels were found to be similar in both groups. As far as we know, the present study is the first to report on intestinal enzyme activity in IC. Because of the limited number of cases, further studies are necessary to determine any relationship between IC and intestinal enzyme activity.

A possible association between IC and later development of asthma or allergic diseases has been the subject of controversy.[14,33,40] The frequency of family history of atopy was similar in both groups in the present study, implying that there is no genetic predisposition in IC cases.

Previously, manipulations of maternal diet to manage IC have been used.[41] When maternal diet was investigated in the present study, tomato and cheese consumption were found to be lower in mothers of colic cases than others in univariable analysis. It is speculated that the antioxidant properties of tomato and cheese might play a preventive role in the occurrence of IC. Tomatoes are a rich source of antioxidants, including vitamin C, lycopene, α- and β-carotene, which have also been proposed to affect the immune function, possibly because of their ability to modulate cellular redox environment and cell-to-cell interaction.[42] Interestingly, Fawzi *et al*.[43] have reported that the dietary intake of tomatoes was inversely associated with total and diarrhea- and, fever-related childhood deaths and with reduced risks of diarrheal and respiratory infection. However, there is no published study about the effect of maternal tomato consumption on IC. Further studies are necessary to clarify the effect of maternal diet on IC.

Sleeping problems were seen more frequently in the IC group in the present study. Multivariable logistic regression analysis revealed that irregular sleeping patterns were seen 2.40 times more in the IC group. Additionally, mothers of the IC group needed an assistant to help their infants sleep more frequently than the NC groups. Consistent with our findings, previous studies have reported that total daily sleep time was shorter in excessively crying infants than in a control group at the age of 6 weeks in a home setting.[44,45] Shorter sleep time could be either a cause or consequence of excessive crying. Previously, later sleeping problems in infants with colic have been suggested.[32,46] However, similar to Kirjavainen *et al*.[44] and Lehtonen *et al*.,[4] our prospective study did not show more sleep problems at 8 months of life in infants with a history of colic compared with the control group. Therefore, we consider that IC does not lead to later sleep difficulties. Interestingly, a previous study reported that colic cases had polygraphic recordings with a normal sleep structure at the age of 9 weeks, indicating that any sleep deprivation during the colicky episodes might not be due to inability to maintain normal sleep structure.[44] Authors explained this controversial result by stressed parents of infants with colic who could have been more sensitive to their infant's night wakings and thus affect daily recordings.[44] However, as a limitation of that study, there was a time gap between the study entry (diagnosis of IC) and the first polygraphic recording.

In the present study, anthropometric measurements at birth and at the second month were similar; however, the mean HAZ score at 7–8 months of age was lower in the IC group than that in the NC group. This is the first study that shows the effect of screaming attacks on HAZ at 7–8 months of age. Crowcroft *et al*.[30] reported that infants with colic were heavier than their control group at birth and the first month. Differences in studies might be explained by the differences in the definition of IC. In a previous study, mothers were only asked whether their baby had colic crying or not. Further studies in infants with colic should be undertaken to determine the differences in growth

parameters including length/height in the long term. However, in the present study higher percentages of maternal smoking during the prenatal period, and sleeping problems at 1.5–2 months of age in IC cases might have an additive negative effect on the growth of infants. Also, more obstructive apnoeas during rapid eye movement sleep in colicky infants[44] at 2 months of age and failure to thrive as a complication of obstructive sleep apnoea[47] might provide possible explanations. Children with obstructive sleep apnoea syndrome and primary snorers have been reported to have lower IGFBP-3 concentrations than control subjects and lower mean relative height than mean target height. These findings suggest that decreased nocturnal GH secretion secondary to sleep pathologies might be responsible for height retardation in IC.

The present study showed no differences in infant development between the two groups in this short-term study period. Formerly, Rao *et al*. reported that cases with excessive crying that persisted beyond 3 months, but not those who had colic only, had poorer outcomes on cognitive development including mean IQ and fine motor abilities at 5 years.[48]

As a limitation of the study, the questionnaire was so long that the mothers could be easily tired. However, our study enabled us to examine, for the first time, many potential risk factors for IC. Our datasets provided comprehensive information regarding infant and maternal characteristics, some of which are difficult to ascertain reliably through maternal interviews. A key strength of our study was that the data were collected prospectively, ensuring that our results were not subject to recall bias. Almost all potential risk factor information was ascertained at the same time or prior to diagnosis with colic and was ascertained similarly for the case and control groups.

In the present study, we conclude that development of colic is associated with some maternal characteristics (maternal education, smoking habits in pregnancy) and the psychosocial environment of infants (domestic violence), maternal hostility scores during early postpartum period and gestational cheese consumption. Addressing these factors and taking steps to change them, including measures to prevent domestic violence, to give up smoking cigarettes and to give social support to mothers may be key points. To decrease IC cases, it is speculated that maternal cheese consumption might be increased during pregnancy. Additionally, having an infant with colic has negatively affected maternal psychological status, and the sleeping pattern of the infant. IC cases were shorter at 8 months of age. The present study is the first to analyse several factors at the same time. Further studies are needed to clarify the interactions of multiple factors affecting IC to enable health workers to manage these cases in a holistic way.

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Competing Interests

None to declare.

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